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Tissue Structure through Diffusion and Transverse Relaxation Measurements

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The unresolved problem: To reveal tissue structure below nominal hardware resolution limits

The goal of MRI is to relate the signal to the tissue structure. The progress in direct visualization of the tissue is bound to slow down as the present hardware is hitting the physiological limits on the spatial resolution of ~1 mm voxel. The challenge lays in the fact that these limits are still 2-3 orders of magnitude greater than the cellular scale, on which the relevant physiological changes occur. Can one, by measuring the MR signal over a macroscopic voxel, uncover the information about the microscopic tissue structure?

Exchange between abstract pools versus realistic models of the tissue structure

At the first glance, the above task is hopeless. Indeed, both the diffusion and the relaxation measurements amount to performing a statistical averaging of tissue properties over a voxel size, giving, at best, the properties of some "average" cell or cluster of cells. This is the philosophy behind the tissue description in terms of models that involve abstract "pools" with exchange rates between them determined from fitting. However, we must keep in mind that the origin of the signal involves a diffusive motion of spins in a real medium whose structure is distributed on the scale of cell size and beyond; thus each spin on its Brownian path explores a particular realization of the tissue structure. The key observation is that the signal, even after averaging over all Brownian trajectories in a voxel, still remains strongly sensitive to the microscopic structure, embodied in the locally varying diffusivity or susceptibility (1,2). The nature of the structure-sensitivity of the diffusion is best illustrated through the mapping between the apparent diffusion coefficient (ADC) and the effective conductivity of a heterogeneous medium with variable local conductivity. It is well known that the conductivity is a strongly structure-specific quantity, highly sensitive to the distribution of the high- and low-conductance regions (3). Remarkably, the transverse relaxation is also highly sensitive to the microscopic distribution of susceptibility (1,4).

Methods: Focus on the statistical description of heterogeneous media

The apparent strong structure sensitivity of the macroscopic tissue characteristics requires rethinking of the way we model diffusion and relaxation. Here we advocate the focus on the structure embodied in the variable components of the local diffusivity $D(\mathbf{r})$ or susceptibility $\chi(\mathbf{r})$. The self-averaging measurement over a macroscopic volume naturally implies the description of the tissue in terms of its statistical characteristics, i.e. the *correlation functions* of $D(\mathbf{r})$ or $\chi(\mathbf{r})$. The technical task is to find the MR signal in terms of these correlation functions (a direct problem), and to infer the information about these correlators from the measured signal (a much harder inverse problem).

Results: Both ADC and T2* depend on the structure

To quantify the structure-specificity we suggest comparing the MR signal to that from a fictitious reference medium (the "soup"), whose $D(\mathbf{r})$ or $\chi(\mathbf{r})$ are completely uncorrelated in space, with the same statistics at each point $\mathbf{r}$. Such a medium can be envisioned as the original tissue cut into small grains that are further randomly mixed. This structureless soup is the analog of the simplest pool models. We find (1,2) that the signals from the realistic medium with spatial correlations present, and from the soup are in general very different, while the short-range part of the correlators give meaning to the parameters of the pool models.

Discussion: The structure-specificity can be either a curse or a virtue: It rationalizes the observed dependece of T2 on the erythrocyte shape (4), giving essential structure-dependent corrections to the predictions of pool-based models. On the other hand, the structure sensitivity provides a possibility, at least in principle, to quantify the tissue characteristics well beyond the spatial limits on resolution if a careful interpretation of the measurements is employed, with a focus on the non-local spatial correlations of the tissue characteristics. In addition to the "extensive" way of improving hardware, we advocate this "intensive" way of relating the signal to the structure. This approach is potentially rewarding from the point of applications. It demands theoretical advances by links to condensed matter physics.

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